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Mortality in Potential Arterial Switch Candidates With Transposition of the Great Arteries

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Objectives. **We reviewed the factors contributing to or causing death before surgery in neonates with d-transposition of the great arteries (TGA) despite anatomy suitable for the arterial switch operation (ASO) to develop strategies to minimize preoperative attrition.**

Background. **Currently the ASO for neonates with TGA carries a low operative mortality. However, there is a paucity of information regarding the patients who die before the ASO. Strategies to ensure survival to operation are of importance to improve overall outcome.**

Methods. **We reviewed all neonates with TGA and patent forearm ovale (PFO) ≤2 mm, a birthweight <2 kg, or who died before surgery, between 1988 and 1996.**

Results. **We identified 12 out of 295 neonates with TGA (4.1%) with anatomy suitable for the ASO who died prior to surgery. All had TGA/intact ventricular septum (IVS) and presented with a severely restrictive PFO. In 11 of 12 cases the cause of death was attributed to the sequelae of profound hypoxemia from inadequate mixing. Contributing factors were prematurity, 41.7%; severe respiratory distress syndrome, 25%; and persistent pulmonary hypertension of the newborn (PPHN), 16.7%. All patients received prostaglandin E1 (PGE1) infusion. Urgent balloon atrial septostomy (BAS) was performed in 66.7% with improved oxygenation. No cases were diagnosed prenatally. In contrast, all patients with a PFO ≤ 2 mm who survived to ASO had a significantly better response to PGE1 infusion (p = 0.03) than nonsurvivors. The ASO was accomplished without mortality in four of nine with a weight <2 kg.**

Conclusions. **Of those neonates admitted with TGA, 4.1% died before surgery. Eleven of 12 (3.7%) died due to consequences of inadequate interatrial mixing despite PGE1 infusion. Earlier diagnosis and BAS are critically important in determining survival. Early ASO may improve survival in patients weighing <2 kg. Prenatal diagnosis with delivery in a high-risk obstetrical unit with facilities for immediate BAS and supportive therapy for pulmonary hypertension and ventricular failure may be necessary to salvage this group of patients.**

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Transposition of the great arteries (TGA) is the most common cyanotic congenital heart defect to present in the newborn (1,2). Attrition without treatment is high and 50% of patients die by the first month of life, especially if the ventricular septum is intact (3). However, balloon atrial septostomy (BAS), the Mustard and Senning procedures, and recently the arterial switch operation (ASO) have changed the outcome dramatically. Indeed, the evolution of the management of TGA culminating in physiological and anatomical correction is a paradigm of success in the treatment of complex congenital heart disease. It was anticipated that the neonatal ASO would overcome important disadvantages of the Mustard and Senning procedures, in particular death before operation, late arrhythmia, and right ventricular failure (4–6). However, examination of the causes and incidence of attrition in neonates before the arterial switch have not been investigated. Therefore, we reviewed retrospectively all neonates with TGA who did not survive to undergo ASO to document the incidence of, and define strategies to minimize, death before operation. In addition, to assess the contribution of a small patent foramen ovale (PFO) and low birthweight to early preoperative death we reviewed the outcome of TGA with either a PFO of ≤2 mm or a birthweight ≤2 kg.

Methods

We began to perform the arterial switch operation in neonates with simple TGA routinely in 1988. We searched the databases of cardiovascular surgery and cardiology of the Toronto Hospital for Sick Children for all neonates admitted between 1988 and 1996 with anatomy suitable for the arterial switch operation. We excluded patients with important ventricular hypoplasia that precluded biventricular repair, and severe pulmonary stenosis or atresia. We analyzed all available clini-

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Abbreviations and Acronyms

ASO = arterial switch operation
BAS = balloon atrial septostomy
IVS = intact ventricular septum
PDA = patent ductus arteriosus
PFO = patent foramen ovale
PGE1 = prostaglandin E1
PPHN = persistent pulmonary hypertension of the newborn
TGA = d-transposition of the great arteries
VSD = ventricular septal defect

cal, echocardiographic, cardiac catheterization, angiographic, and autopsy data.

We imaged the atrial septum by echocardiography from the subcostal short axis view and measured the widest interatrial communication during the cardiac cycle. We imaged the patent ductus arteriosus (PDA) from the suprasternal or high parasternal window and recorded the narrowest dimension with on-line calipers and the direction of flow by Doppler interrogation.

Pulmonary hypertension was diagnosed either by the presence of reverse differential cyanosis, or a ductal shunt predominantly from pulmonary artery to aorta by echocardiography or histologically at autopsy.

Statistical analysis. As the sample size was small and the data not normally distributed the nonparametric Mann-Whitney U test was used to compare differences between patients who survived and those who died before surgery. A p value of <0.05 was considered significant.

Results

We admitted 295 neonates with TGA and anatomy suitable for the arterial switch operation between 1988 and 1996. Twelve patients (4.1%) died prior to surgery. Their perinatal and postnatal data are summarized in Table 1.

Echocardiographic features. All 12 patients had TGA with intact ventricular septum and severely restrictive foramen ovale (0–2 mm). Obvious bowing of the interatrial septum (IAS) into the right atrium was evident in nine of 12 patients. We detected an aneurysm of the IAS in three of 12 and reduced biventricular function in another three patients.

Response to prostaglandin PGE1. Eleven of 12 patients received PGE1 at the referring institution, before the arrival of the transport team, at the initial rate of 0.1 μg/kg/min but only two responded with a rise in oxygen saturation of 10% or more. One patient did not receive PGE1 until the arrival of the transport team because it was unavailable at the referring hospital.

Transportation. The median time between arrival of the transport team at the referring hospital and admission to the Hospital for Sick Children in Toronto was 3.5 h, with a range of 2–6 hours.

Balloon atrial septostomy (BAS). Emergency BAS was performed in eight of 12 patients (four of eight in the cardiac catheterization laboratory and four of eight on the intensive care unit under echocardiographic guidance). One patient (patient 6), with a weight of 1740 g and respiratory distress syndrome of prematurity, remained persistently desaturated 4 d after BAS. He was considered too small and premature for an arterial switch at that time and underwent Blalock-Hanlon septectomy. In all eight cases an adequate sized atrial communication was created, either by balloon or surgically, as judged by oxygen saturation (>75%), echocardiogram, surgical inspection, and/or autopsy. Median atrial septal defect size was 8 mm (range 8–13 mm). There were no complications associated with BAS. Four patients died without BAS at median age of 10 h (range 9–15 h). All four were admitted before we performed BAS routinely on the intensive care unit. Two

Table 1. Perinatal and Postnatal Data

Case No.	Birth weight (kg)	Gest Age (wk)	Apgar Score	Art O_2 Sat (%)	Age PGE Started (h)	Transport Time (h)	PFO (mm)	PDA (mm)	Age at BAS	Associated Conditions	Age at Death
1	3.8	37	7,7	20	6	5	1.2	3.2	18 h	PPHN	5 d
2	3.1	38	5,5	40	8	3	1.3	3.7	N/D	DIC, pulmonary hemorrhage	12 h
3	1.3	28	3,8	60	12	2	1.5	4.0	N/D	Sepsis, seizure	15 h
4	3.8	37	8,3	50	5	5	1.5	3.5	13 h	MAS, PPHN	4 d
5	1.4	32	8,8	70	9	4	1.3	2.2	17 h	Tracheal stenosis	21 d
6	1.7	32	6,7	60	48	2	2.0	3.8	8 d	RDS, NEC	14 d
7	3.7	39	3,5	30	2	5	0.0	3.5	N/D	MAS, reduced bivent fxn.	9 h
8	3.0	40	9,9	30	16	2	1.3	3.2	20 h	Sepsis, reduced bivent fxn	3 d
9	1.4	28	5,6	30	4	3	1.4	2.5	N/D	RDS, sepsis	10 h
10	2.9	39	7,7	30	5	6	1.3	3.8	11 h	Seizure, renal failure	10 d
11	1.7	32	6,7	60	8	3	1.3	2.2	19 h	Sepsis	25 d
12	2.5	38	5,6	60	2	5	1.2	5.0	13 h	Seizure, IVH, reduced bivent fxn	3 d
Median	2.7	37		45	7	4	1.3	4	17.5 h		3.5 d

DIC = disseminated intravascular coagulopathy, Gest = gestational, IVH = intraventricular hemorrhage, MAS = meconium aspiration syndrome, N/D = not done, NEC = necrotizing enterocolitis, PPHN = persistent pulmonary hypertension of the newborn, RDS = respiratory distress syndrome, bivent fxn = biventricualr function.

patients were considered too small (1300 and 1400 g) for BAS at the time and two patients (one with a completely intact atrial septum) were considered so profoundly damaged by hypoxemia and low cardiac output that it was elected not to pursue further aggressive management. They both died within 2 h of admission.

All 12 patients received supportive therapy prior to and during transportation with 5–15 μg/kg/min of dopamine, mechanical ventilation to abolish respiratory acidosis if possible, supplemental oxygen, and treatment of metabolic acidosis with fluid and sodium bicarbonate. In addition, hypoglycemia, hypocalcemia, and hypothermia were corrected. All patients were paralyzed and sedated. On admission and after confirmation of diagnosis and associated medical problems therapy was tailored accordingly. No patient received inhaled nitric oxide therapy or mechanical support of the circulation preoperatively.

Associated medical problems (Table 1). Associated medical problems indicative of perinatal stress were frequent and included respiratory distress syndrome, pulmonary hypertension, sepsis, and neurological injury (intraventricular and cerebral hemorrhage, and seizure activity). In contrast, additional congenital malformations were uncommon. One patient had congenital tracheal stenosis with complete cartilagenous rings.

Prematurity and low birth weight. Between 1988 and 1996 we admitted nine patients with TGA and prematurity (3.05% of TGA) and low, but appropriate, birth weight (<2 kg) for gestational age. Four (three with TGA/intact ventricular septum [IVS] and one with TGA ventricular septal defect [VSD] and coarctation of the aorta) underwent arterial switch operation, performed in three with TGA/IVS between days 3 and 8 of life and on day 43 in the patient with TGA/VSD after prior coarctation repair and pulmonary artery band on day 12 of life, without surgical mortality. Five patients who were managed expectantly died prior to surgery. Comparison of group 1 (death before operation) versus group 2 (survival to surgery) demonstrated no statistical difference in gestational age ($p = 0.14$) or birth weight ($p = 0.14$). However, group 2 had a statistically significant higher initial oxygen saturation ($p = 0.04$), larger atrial communication ($p = 0.01$), and better response to prostaglandin infusion ($p = 0.03$).

Autopsy data. Autopsies were performed in six of 12 cases (patients 1, 2, 3, 4, 6, and 8). All had PDA (median size 5.5 mm, range 4–8 mm). A restrictive PFO was found in all patients who did not undergo BAS. Additional autopsy findings were pulmonary hypertension (thickening of intima and media of pulmonary arteries in two of six), disseminated intravascular coagulopathy (fibrin platelet microthrombi in pulmonary vessels in two of six), pulmonary hemorrhage (two of six), and intracranial hemorrhage (four of six). Patient No. 5 had a perforation of the trachea following surgery for congenital tracheal stenosis.

Comparison with survivors to ASO. We identified eight neonates with TGA and a PFO ≤2 mm who survived to ASO after BAS. All had TGA with IVS. They had significantly higher oxygen saturations after infusion of PGE1 (median 68%, range 35–80 vs median 50%, range 30–70, $p = 0.03$), wider PFO (median 1.9 mm, range 1.4–2.0 vs median 1.3, range 0–2.0, $p = 0.003$), larger PDA (median 4.5 mm, range 3.5–5.8 vs median 3.5, range 2.2–5.0, $p = 0.01$) and shorter transport times (median 0.6 h, range 0.2–5 vs median 3.5 h, range 2–6, $p = 0.004$). There was no statistical difference between birthweight (median 3200 g, range 2830–3700 vs median 2720 g, range 1300–3800, $p = 0.2$) but the gestational age was older (median 40 wk, range 38–42 vs median 39 wk, range 28–39, $p = 0.001$). There were no statistical differences in oxygen saturations before infusion of PGE1 (median 45%, range 20–70 vs median 55%, range 25–72, $p = 0.33$) or age that PGE1 was started (median 3.8 h, range 1–13.7 vs median 7 h, range 2–48, $p = 0.14$) or age at BAS (median 15.5 h, range 5–20 vs median 17.5 h, range 11–192 $p = 0.31$).

None of the eight patients developed metabolic sequelae of hypoxemia (acidosis, hypoglycemia, or hypocalcemia) and only two of eight required inotropic support (5 μg/kg/min dopamine).

The shunt through the PDA was predominantly from aorta to pulmonary artery in all patients as described by Baylen et al (7). In contrast two of 12 nonsurvivors had bidirectional shunts with right to left shunting throughout systole and into diastole. BAS was performed in the cardiac catheterization laboratory in four of eight and on the intensive care unit in four of eight.

Discussion

As the surgical results for the ASO continue to improve and operative mortality falls below 3%, strategies to salvage patients at risk of death before surgery are of paramount importance to reduce the overall mortality of TGA (8). Although death before operation was recognized as an important disadvantage of atrial redirection surgery for TGA (a mortality of 11%), there is a paucity of information regarding very early death in babies with TGA since the shift in management to neonatal arterial switch surgery (4,6,9). Our study demonstrates that death before surgery is substantial, especially when it is compared with the excellent short and long-term survival with the arterial switch procedure (8,10). The preoperative mortality rate in the present study is comparable with the 3.7% (35/946 neonates with TGA admitted under 15 days of age) reported by Kirklin et al. (8). However, preoperative attrition rates have improved from 16% of all transpositions between 1979 and 1983 reported by Gilljam and 11% of simple transpositions between 1976 and 1983 reported by Trusler et al (6,11). In addition, we suggest that hypoxemia and its sequelae, especially if the PFO is restrictive, the need for transport to a cardiac center, the lack of response to PGE1, low birthweight, and prematurity are important contributors to preoperative mortality. Extracardiac anomalies are rare in TGA and resulted in one death in our series prior to operation (1,3). Therefore, strategies to improve overall survival should examine earlier diagnosis and balloon atrial septostomy, as

well as the influence of prematurity, low birth weight, and pulmonary hypertension in more detail.

Earlier diagnosis. All patients who died required more aggressive supportive therapy prior to transport and had significantly longer transport times compared with survivors. In addition, eight patients in our study died despite BAS, suggesting that for some neonates there is a window of time within which an atrial septostomy must be performed to avoid permanent organ damage and death. This will require an emphasis on prenatal screening and timely transport of the mother to a tertiary care center before delivery. In the unusual case when the diagnosis is made by echocardiography at the referral center, it may be prudent to send a cardiologist to perform a BAS prior to transportation, especially if there is minimal improvement in systemic oxygen saturations with an infusion of prostaglandin or evidence of important restriction to interatrial mixing by echocardiography. However, we have experience with a term baby with TGA/IVS, a restrictive PFO, and PDA diagnosed prenatally who died in the delivery room (12). It is notable that in the NERICP report by Fyler et al, five of 236 patients with TGA presented at autopsy without prior cardiac catheterization and Trusler et al noted three neonates, moribund on admission, who died within a few hours of birth (1,6). Therefore, there may be a subset of patients with TGA/IVS with tenuous intercirculatory mixing in utero who may be salvageable only by immediate BAS, perhaps even in the delivery room and prior to separating the umbilical cord or immediate cannulation for mechanical cardiopulmonary support.

While many patients with TGA benefit from PGE1 to increase ductal flow, left atrial blood return, and mixing at atrial level, paradoxically, those with restrictive atrial communications may become more cyanosed as left atrial hypertension closes further the flap of the foramen ovale, decreases atrial mixing, reduces effective pulmonary flow, and results in pulmonary edema (7). Prostaglandin infusion, prior to BAS, was unsuccessful in improving oxygen saturation in most of our patients who died. In contrast, survivors to ASO with a small PFO responded with a significantly higher oxygen saturation. Failure to respond to PGE1 infusion should alert all concerned that rapid transport and BAS may be required. The importance of adequate intercirculatory mixing is emphasized by the observation that all preoperative deaths occurred in patients with an intact ventricular septum.

Prematurity and low birth weight. Prematurity is uncommon in TGA (3). We found an incidence of 3.05%. The size of the native atrial communication, an increase in oxygen saturation in response to prostaglandin, and early ASO differentiated those who survived from those who died. Indeed, the confounding management problems of low birth weight and prematurity may be simplified if surgical corrections of anatomy and physiology are undertaken. Continued technical and surgical advances, and our experience, suggest that the low birthweight and premature neonate with congenital heart disease may fare better with early correction rather than prolonged medical supportive management waiting for growth (13,14).

Associated medical problems. The associated medical problems that complicated management (meconium aspiration syndrome and persistent pulmonary hypertension) were indicative of perinatal stress. The exact incidence of prenatal restriction at ductal or atrial level that may compromise the newborn with TGA and lead to rapid and critical hypoxemia shortly after umbilical cord clamping remains unknown. However, our recent experience suggests that it may occur (12). Improvements in fetal surveillance with prenatal transfer of at-risk mother and fetus to a tertiary care center with facilities for early BAS will be required.

Persistent pulmonary hypertension. Persistent hypoxemia, especially in the upper body, after BAS and despite prostaglandin infusion may be due to persistent pulmonary hypertension of the newborn complicating TGA (15,16). Recent reports suggest that a brief period of stabilization, alkalinization, and early ASO, with inhaled nitric oxide therapy pre and postoperatively may be a successful strategy to salvage this subgroup of neonates with TGA (16–18). Inhaled nitric oxide therapy improves oxygenation in neonates with persistent pulmonary hypertension of the newborn (PPHN) (19) and has been useful in TGA/IVS and PPHN with predominant right to left shunting at ductal level and hypoxemia despite BAS (17). In refractory cases and especially if there is ventricular dysfunction, the use of extracorporeal cardiopulmonary support may be lifesaving as reported by Luciani et al (17), although the high incidence of cerebral hemorrhage may limit the use of mechanical cardiopulmonary support. However, despite the neonatal arterial switch, patients with TGA may develop pulmonary vascular disease (20) and the presence of irreversible pulmonary vascular changes at birth may limit the efficacy of therapy in some cases.

Conclusion. We found that 4.1% of neonates with TGA died before surgery. In 11 of 12 patients death was due to consequences of inadequate interatrial mixing despite prostaglandin infusion. Earlier diagnosis and balloon atrial septostomy are critically important in determining survival. We suggest that, in the neonate with TGA/IVS, failure to respond to PGE1 infusion defines a patient with inadequate atrial mixing who should be urgently and rapidly transferred for immediate BAS. Even with prenatal diagnosis of TGA/IVS, prediction of postnatal instability may be difficult. Therefore, we suggest that prenatal diagnosis of TGA/IVS be accompanied by delivery in a high-risk obstetrical unit with adjoining facilities for immediate balloon atrial septostomy, and, if necessary, supportive treatment of PPHN and ventricular failure (including inhaled nitric oxide and mechanical cardiopulmonary support), to salvage this group of patients.

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